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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,288	07/06/2001	Paul F. Goetinck	10284-029001 / MGH 1733.1	6095

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 07/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,288	GOETINCK, PAUL F.9	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-11 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-11 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 4/28/2003 (paper no 12) is acknowledged and entered into the record. Accordingly, claims 2-6 and 12-16 are canceled, and claims 17-19 are newly added.

2. Therefore, claims 1, 7-11, and 17-19 are pending and examined on the record.

Claim Rejections Withdrawn - 35 USC § 112, 2nd paragraph

3. The rejection of claims 1 and 7-11 under 35 USC 112, 2nd paragraph is withdrawn in view of the arguments provided by the applicant.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 1, 7-11, and now newly added claims 17-19 under 35 USC 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record. Additional arguments are provided in the instant Action to substantiate the lack of enablement. Applicant argues that the working example of an in vivo transgenic mouse model proves that the reduction of syndecan-4 inhibits angiogenesis. Applicant further argues that "a skilled artisan could predict that the recited agents which decrease the expression, level, or activity of syndecan-4 would inhibit angiogenesis." Applicant's arguments have been carefully considered but are not found persuasive. The instant specification discloses the generation of syndecan-4 -/- homozygous transgenic mice. Applicant states that because the "recited agents" (i.e. nucleic acids that bind to syndecan-4 mRNA, nucleic acids that are complementary to syndecan-4

cDNA, or antibodies that specifically bind to syndecan-4) were known at the time of filing and that the use of such said agents is considered routine in the art, one of skill in the art would be able to extrapolate positive inhibitory effects with said agents based on the data collected from the transgenic animal model. However, such interpretations are often unpredicatable and unreliable.

Mak et al. (Nat. Rev. Immunol. 2001; 1:11-19) review that although gene-targeting has provided great insights into gene function, there are caveats that must be considered when assessing the phenotypes of genetically engineered mice (see entire reference, but especially the bridging paragraph of pages 13 and 14). In particular, Mak et al. note that engineered mutations in one gene can affect the expression of unaltered neighboring genes, giving rise to phenotypes that are unconnected to the gene of interest; and that gene deletions can also affect the architecture of an organ, such as the lymph nodes or spleen, which would have secondary effects on cells within these organs. Mak et al. conclude that there is a danger that such effects might be misinterpreted as primary effects of the gene mutation on the cells themselves.

Chang H *et al* (Mol. Cell. Endocrinol.) (Ireland) 2001; 180(1-2):39-46) disclose a knockout of a component of the TGF-β signal transduction cascade, and conclude that "the expression pattern of a component in a TGF-superfamily signal transduction cascade does not necessarily predict its in vivo function" (see abstract).

Although the specification discloses that a genetic inactivation of syndecan-4 in mice inhibits angiogenesis; it is unpredictable if these phenotypes are due directly to inactivation of syndecan-4. Consequently, it would require undue experimentation of

the skilled artisan to establish that the phenotype observed in the syndecan-4 null mouse was a direct consequence of inactivation of the gene encoding syndecan-4 or if such effects are directly correlative to its actual in vivo function. Therefore, in the absence of such objective evidence the application of syndecan-4 reducing agents in the instantly recited methods would be highly unpredictable. The skilled artisan cannot predict with any certainty that the agents claimed would function in a manner similar to that exemplified by the syndecan-4 null mouse model. Even assuming that the efficacy of agents claimed were predictable based on the results obtained from the transgenic mouse model, the art at the time of filing had not established with any certainty the predictability and feasibility of using the reducing agents in inhibiting angiogenesis in subjects.

Kerbel R *et al* (Nat. Rev. 2002;2:727-739) review that the use of anti-angiogenesis drugs can potentially provide a new class of drugs which are less toxic and less drug resistant for the treatment of cancer. However, there are many challenges and factors that must be determined before such treatment is effective. For example, Kerbel R *et al* state that some drugs when administered to subject can "induce stable disease" (see page 729), while others induce tumor regression. They also state that many challenges exist for the use of anti-angiogenesis treatment, such as the availability of "markers of efficacy" and the need for further research in understanding the mechanism of some anti-angiogenesis drugs (see page 736). In particular, Kerbel R *et al* cite conflicting results of one particular gene therapy approach of the anti-angiogenesis drug endostatin (the delivery of an adenovirus expressing endostatin was

ineffective in reducing tumor growth, whereas the direct transfection of endostatin into tumor cells completely inhibited tumor growth in a mouse) (page 736).

Therefore, given the unpredictable nature of the anti-angiogenesis drugs in general and the unpredictable nature of the agents themselves, one of skill in the art cannot predict with any certainty that the method as claimed would inhibit angiogenesis based on the data disclosed from the transgenic animal model disclosed. As a result the skilled artisan would be forced into undue experimentation to practice the instant invention commensurate in scope to the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
July 9, 2003